

Health Disparities in Screening, Diagnosis, and Treatment of Hepatocellular Carcinoma

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This is an updated review on health care disparities in the screening, diagnosis, and treatment of hepatocellular carcinoma (HCC). Worldwide, HCC remains a leading cause of cancer-related death, ranking fourth in mortality and sixth in incidence with significant variation among different regions.¹ The highest rates of HCC are seen in East Asia, Asia Pacific, and central sub-Saharan Africa. However, with hepatitis B virus (HBV) vaccination, as well as antiviral therapy for HBV and hepatitis C virus (HCV), decreasing incidence of HCC is now being seen in Japan and China.¹ In contrast, the incidence in North America and certain parts of Europe has steadily increased, likely related to increasing rates of obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD).¹ The degree to which these and other risk

factors for HCC contribute to overall disease burden varies by sex, as well as by race and ethnicity.

Recent epidemiological data from the United States indicate a plateauing incidence of liver and intrahepatic bile duct cancers, a category composed largely of HCC (Fig. 1).² Despite this trend, however, several groups remain at disproportionate risk. Recent studies show stabilizing HCC incidence, increasing just 0.7% from 2010 to 2012 and accompanied by decreasing incidence among Asian Pacific Islanders (APIs) and patients younger than 65 years.^{3,4} Projections based on current data predict that by 2030 incidence among minorities will stabilize in Hispanic individuals and decline particularly among male

Abbreviations: A1AT, alpha-1-antitrypsin deficiency; AIH, autoimmune hepatitis; API, Asian Pacific Islander; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LA, liver ablation; LR, liver resection; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; PAF, population-attributable fraction; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SEER, Surveillance Epidemiology and End Results; SES, socioeconomic status; SNH, safety net hospital.

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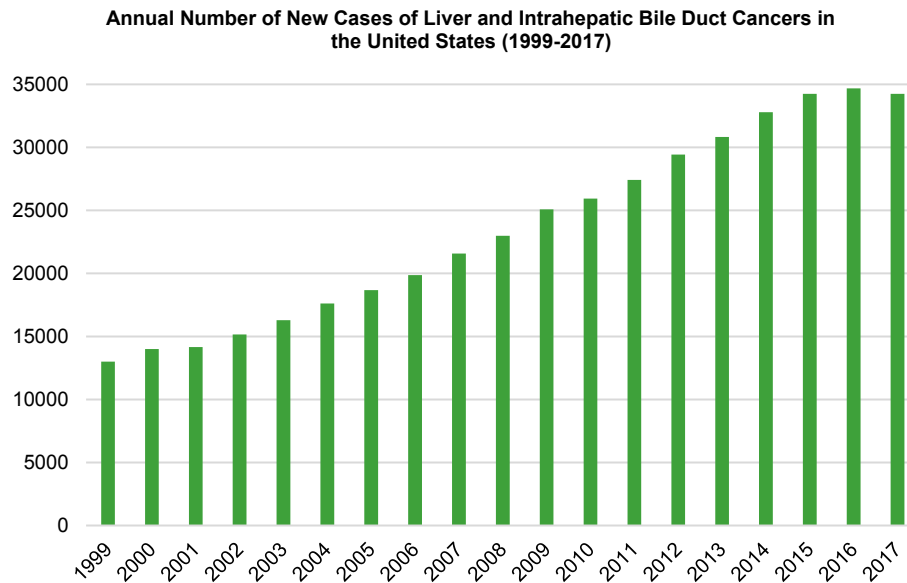


FIG 1 Annual number of new cases of liver and intrahepatic bile duct cancers has plateaued in recent years. Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2020..2.

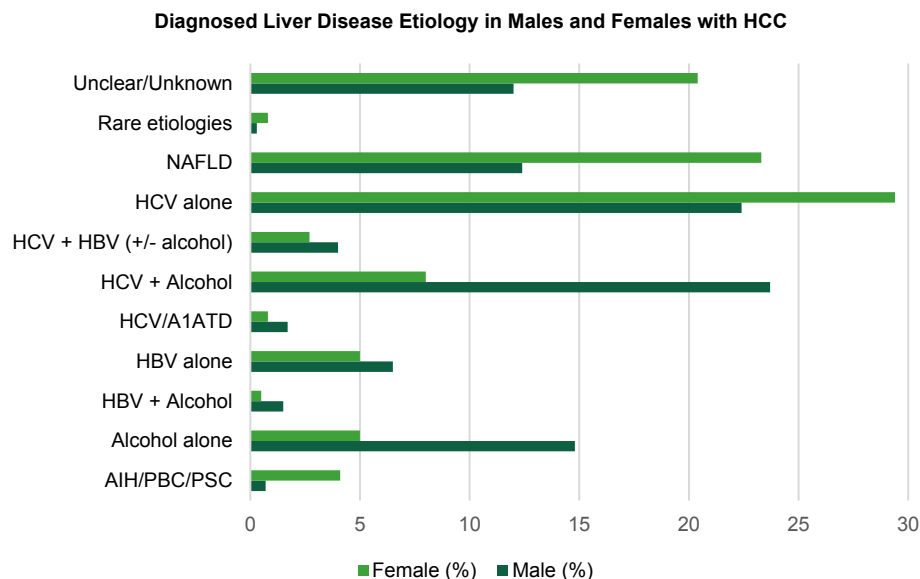


FIG 2 Significant differences in disease etiology between sexes. Women with HCC have a significantly greater frequency of NAFLD and noncirrhotic HCC. Adapted from *American Journal of Gastroenterology*.⁷ Copyright 2020, American College of Gastroenterology.

APIs.³ Incidence among white individuals is expected to increase, although rates among black and Hispanic individuals will remain disproportionately high.³ By sex, the 2030 predicted incidence is expected to be highest in black women and Hispanic men.³ These stable incidence projections may be limited because of an anticipated increase in risk among younger cohorts potentially associated with increasing rates of obesity and NAFLD.⁵

Targeting prevention and detection efforts toward populations anticipated to be at the greatest risk thus remains imperative.

DISPARITIES RELATED TO SEX

Men continue to have significantly greater rates of HCC compared with women in a ratio of 3:1 to 4:1. The precise

contributors to this disparity have yet to be identified.^{6,7} Plausible factors include behavior, underlying disease etiology, immune responses, epigenetics, and sex hormone interactions with viral replication.¹ Comparing population-attributable fractions (PAFs) for various risk factors, metabolic disorders are the greatest contributor to HCC in both sexes, while women have a higher PAF of HCV and men have a higher PAF of alcohol-related disorders.⁸ In regard to underlying cause of liver disease, a recent systematic review and meta-analysis suggests that in the general population, women have a lower risk for NAFLD compared with men but a greater risk for disease progression after the development of NAFLD.⁹ Complementing these findings, a recent large retrospective multicenter study in the United States shows that among patients with HCC, women have a significantly greater frequency of both NAFLD and noncirrhotic HCC, with the latter also believed to be related to underlying NAFLD (Fig. 2).⁷ Comparatively, the most common disease causative factors among men with HCC in this cohort are HCV and alcohol use, either alone or concurrently.⁷ These findings underscore the need for accurate phenotyping in the study of HCC, both to further elucidate underlying disease states and to help guide public health policies.

Persistent disparities in screening and diagnosis between the sexes, for instance, have yet to be fully explained. Data from single-center retrospective studies suggest that women are more likely to be diagnosed on routine screening and men are more often diagnosed incidentally or with symptoms.^{10,11} This in part may explain why men tend to have larger tumors (>5 cm) and more severe disease (stage III or IV) at diagnosis, whereas women are less likely to present in a decompensated disease state.^{7,11,12}

These differences in disease detection likely translate to significant differences in HCC treatment. Recent data suggest that women are more likely to undergo liver resection (LR) or liver ablation (LA) and less likely to undergo liver transplantation (LT) compared with men.^{7,10,12} This preference for less costly noncurative procedures for women may be attributed to greater rates of adherence to routine screening recommendations, which likely result in earlier disease detection and thus better comparative functional status at diagnosis with less advanced disease and slower disease progression.¹² Data regarding decision making, however, are limited. Lower rates of cirrhosis in women may also contribute to reduced rates of LT.⁷ In terms of

outcomes, women have greater overall survival and a lower risk for inpatient mortality, which may be related to lower rates of 30-day mortality in LR and LA compared with LT.^{7,12}

These data suggest the need for sex-specific screening strategies guided by the identification of common risk factors and underlying causes of liver disease. Increased vigilance among men may be warranted to avoid under-screening. Prevention efforts focused on metabolic disorders will likely benefit both sexes. Such improved screening and prevention efforts will likely alter the landscape of treatment modalities among men and women, perhaps resulting in less advanced disease at diagnosis overall and more equal rates of LR, LA, and LT.

DISPARITIES RELATED TO RACE AND ETHNICITY

HCC is seen at higher rates among Hispanics, blacks, and APIs compared with non-Hispanic whites. Within these groups, there has been a dramatic increase in incidence of HCC among Hispanic individuals, about 4.7% per year since 2000, with decreasing incidence among APIs.¹³ The increase in incidence among Hispanics has been attributed to HCV, NAFLD, alcoholic liver disease, higher rates of metabolic syndrome, and a likely genetic predisposition for fatty liver and disease progression.^{1,14,15} Calculated PAFs for HCC risk factors show that metabolic disorders have the greatest contribution to disease burden in Hispanic and white individuals, whereas HCV has the greatest contribution in black and Asian individuals.⁸ A recent systematic review and meta-analysis showed that the prevalence of NAFLD is highest in Hispanic and lowest in black individuals.¹⁶ Further conclusions on differences in NAFLD severity and prognosis among racial/ethnic groups, however, are limited by discordant data.¹⁶ In terms of HCC disease severity at presentation, it has been noted that compared with white individuals, black individuals have greater tumor burdens with higher rates of infiltrative HCC and distant metastases.^{1,13,15}

In addition to being associated with significant epidemiological differences, race and ethnicity are known risk factors for reduced or delayed health care utilization for the screening, diagnosis, and treatment of HCC.^{13,17} A large retrospective study of patients with HCC in two large urban health systems shows that a similar proportion of HCC was detected by surveillance among whites and nonwhites, but that whites are more likely to receive

hepatology-focused care in the year prior to diagnosis. Black and Hispanic patients are less likely than white patients to be diagnosed at tumor stage Barcelona Clinic Liver Cancer (BCLC) 0/A, with reduced screening rates explaining the difference seen among black patients, but not among Hispanic patients.¹³

In terms of treatment, Hispanic patients are less likely to receive HCC-directed, curative therapy at BCLC stage 0/A HCC.¹³ A large retrospective cohort study using the Surveillance Epidemiology and End Results (SEER) database notes that black and API patients are less likely to undergo LT but more likely to received LR compared with white patients. Hispanic patients are less likely to receive LR and LA.¹⁸ These findings may be related to limitations in access to care, as well as regional variations in practice pattern and organ availability.¹⁸ A contemporary population-based study conducted using a comprehensive US state cancer registry, for example, shows that Hispanic and black patients are more likely to be evaluated at safety net hospitals (SNHs), which is associated with increased mortality.^{13,19} These differences in disease detection and treatment likely contribute to the reduced median overall survival observed in Hispanic and black patients compared with white patients (Fig. 3).¹³

Disparities related to race and ethnicity thus stem from environmental, social, economic, and biological variables that influence both the distribution of risk factors

contributing to disease burden and the allocation of resources governing HCC treatment and prevention. Given the complexity of these interactions, further concerted efforts to pinpoint and address the underlying causes of observed disparities at each of these levels will be necessary to achieve equity, access, and improved outcomes.

DISPARITIES RELATED TO SOCIOECONOMIC STATUS

HCC has been shown to disproportionately affect individuals of low socioeconomic status (SES), with lower observed surveillance and survival rates in those with the lowest income.^{20,21} A large retrospective study using the SEER database shows that increasing degrees of poverty are associated with reduced survival rates. High-poverty individuals have the lowest 6-, 12-, and 24-month relative survival rates, and low-poverty individuals have the highest relative survival rates.²² The authors also note that this survival gap has increased with time, widening from 1983-1992 to 2003-2012 (Fig. 4).²² This suggests the need for enhanced efforts to intervene on the specific factors suspected of contributing to this disparity.

Several patient-level factors may lead to lower surveillance rates and late-stage detection of HCC. A survey conducted in a large urban hospital among patients with cirrhosis with diverse racial and socioeconomic backgrounds revealed that although patients had a high

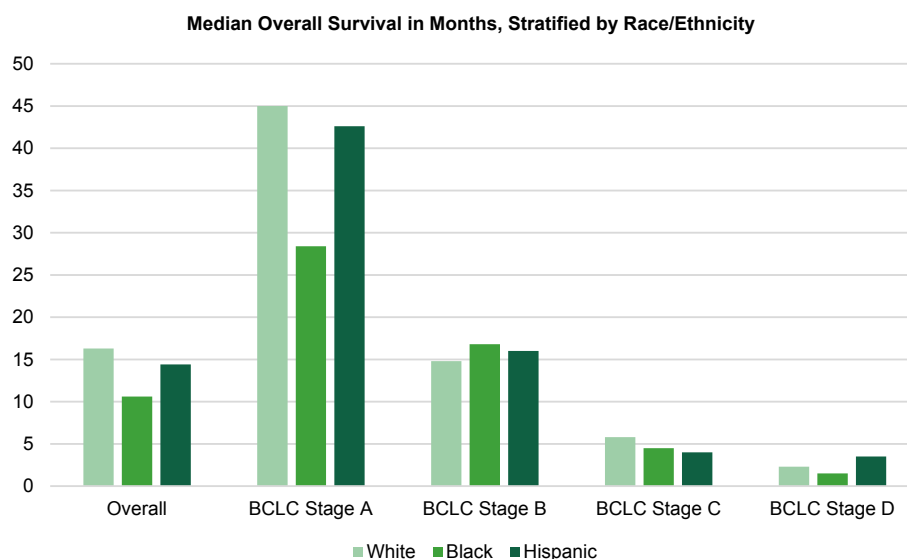


FIG 3 Median overall survival was reduced in Hispanic (14.4 months at all BCLC stages) and black patients (10.6 months and most pronounced in BCLC stages A and D) compared with white patients (16.3 months). Adapted with permission from *Clinical Gastroenterology and Hepatology*.¹³ Copyright 2019, American Gastroenterological Association.

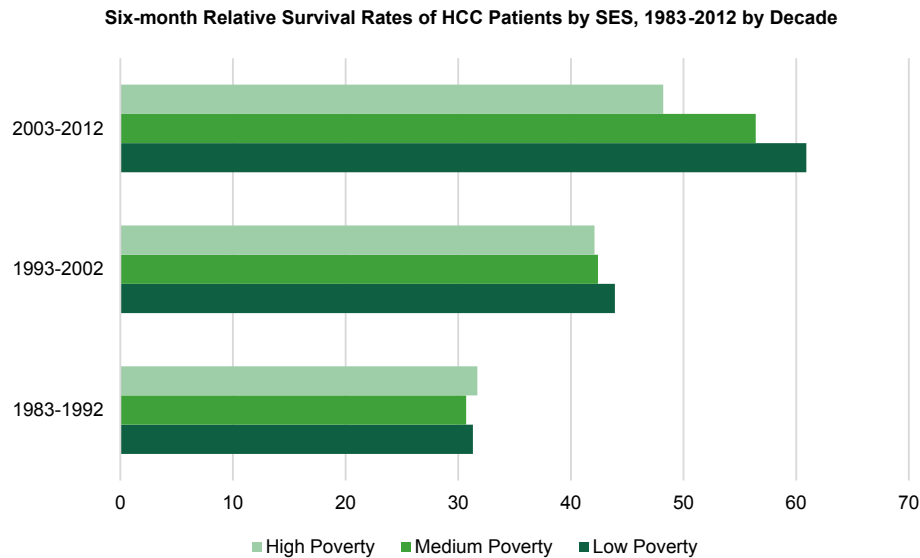


FIG 4 High-poverty individuals had the lowest relative survival rates, and low-poverty individuals had the highest relative survival rates with the survival gap widening from 1983-1992 to 2003-2012. Adapted from *Oncotarget*.²² Copyright 2016, Impact Journals LLC.

degree of HCC-related knowledge, a significant knowledge gap was noted in relation to HCC surveillance, as well as treatment logistics and effectiveness.²³ Many cited cost of surveillance studies, scheduling issues, and transportation challenges as barriers to receiving care.²³ This suggests that targeted patient education and logistical optimization to remove patient-level barriers are important areas of focus for initiatives aimed at improving surveillance rates.

At the systems level, this difference in survival may be related to variation in health care access and delivery. Uninsured patients and those with Medicaid are more likely to have advanced disease and less likely to receive LR or LT compared with those with Medicare or commercial insurance. These patients also have significantly lower survival rates.²⁴ Moreover, a large proportion of uninsured and underinsured patients, as well as other disadvantaged groups, are evaluated in SNHs, which have been linked to worse outcomes and lower rates of curative HCC treatment even at early-stage diagnosis.¹⁹ SNHs are, of course, essential providers of health care for an ever-growing population of patients, especially following expanded insurance coverage under the Patient Protection and Affordable Care Act in the United States. Although SNHs and non-SNHs have similar transplantation, oncology, and radiology resources, there may be limited access to HCC specialized providers, particularly

for uninsured or underinsured patients.¹⁹ Additional studies assessing factors such as clinic capacity, operating room capacity, patient panel size, and level of nursing support are needed.

Overall, it is clear that this continues to be an area of active investigation with a lack of notable improvements in outcomes for low-SES patients. Additional studies examining patient, provider, and systems-level factors contributing to SES disparities will be necessary to help develop public health interventions and shape public policy.

CONCLUSION AND FUTURE DIRECTIONS

Recent data provide important insights into current and potential future trends in HCC, allowing for the development of targeted interventions to address persistent health care disparities, particularly among Hispanic, black, and low-SES individuals. Special attention should also be paid to emerging disease causative factors, namely, obesity and NAFLD, which threaten to undo much of the progress that has been made in reducing the incidence HCC. Many of the current studies with the largest cohorts are retrospective and limited by their use of the SEER database, which has limited resolution in terms of disease etiology and risk factors. Efforts toward uncovering the underlying causes of known disparities will require prospective data that are more granular in nature. Continuing to highlight these

differences will provide opportunities to develop structural changes, as well as tailored clinical approaches, in an effort to reduce disparities.

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REFERENCES

- 1) El-Serag HB. Epidemiology of hepatocellular carcinoma. In: Arias IM, Alter HJ, Boyer JL, eds. *The Liver: Biology and Pathobiology* [Internet]. 6th ed. Wiley; 2020:758-772. Available at: <https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119436812.ch59>.
- 2) U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2020. Available at: <https://www.cdc.gov/cancer/dataviz>.
- 3) Petrick JL, Kelly SP, Altekruse SF, et al. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. *J Clin Oncol* 2016;34:1787-1794.
- 4) White DL, Thrift AP, Kanwal F, et al. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology* 2017;152:812-820.e5.
- 5) Beal EW, Tumin D, Kabir A, et al. Cohort contributions to race- and gender-specific trends in the incidence of hepatocellular carcinoma in the USA. *World J Surg* 2018;42:835-840.
- 6) McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2015;19:223-238.
- 7) Phipps M, Livanos A, Guo A, et al. Gender matters: characteristics of hepatocellular carcinoma in women from a large, multicenter study in the United States. *Am J Gastroenterol* 2020;115:1486-1495.
- 8) Makarova-Rusher OV, Altekruse SF, McNeel TS, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States: US HCC-Attributable Risk Factors. *Cancer* 2016;122:1757-1765.
- 9) Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women have a lower risk of nonalcoholic fatty liver disease but a higher risk of progression vs men: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020. Available at: <https://doi.org/10.1016/j.cgh.2020.04.067>.
- 10) Wu EM, Wong LL, Hernandez BY, et al. Gender differences in hepatocellular cancer: disparities in nonalcoholic fatty liver disease/steatohepatitis and liver transplantation. *Hepatoma Res* 2018;4:66.
- 11) Ladenheim MR, Kim NG, Nguyen P, et al. Sex differences in disease presentation, treatment and clinical outcomes of patients with hepatocellular carcinoma: a single-centre cohort study. *BMJ Open Gastroenterol* 2016;3:e000107.
- 12) Sobotka L, Hinton A, Conteh L. Women receive more inpatient resections and ablations for hepatocellular carcinoma than men. *World J Hepatol* 2017;9:1346-1351.
- 13) Rich NE, Hester C, Odewole M, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2019;17:551-559.e1.
- 14) Rotman Y, Koh C, Zmuda JM, et al; the NASH CRN. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. *Hepatology* 2010;52:894-903.
- 15) Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology* 2019;156:477-491.e1.
- 16) Rich NE, Oji S, Mufti AR, et al. Racial and ethnic disparities in non-alcoholic fatty liver disease prevalence, severity, and outcomes in the United States: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;16:198-210.e2.
- 17) Xu L, Kim Y, Spolverato G, et al. Racial disparities in treatment and survival of patients with hepatocellular carcinoma in the United States. *Hepatobiliary Surg Nutr* 2016;5:43-52.
- 18) Peters NA, Javed AA, He J, et al. Association of socioeconomic, surgical therapy, and survival of early stage hepatocellular carcinoma. *J Surg Res* 2017;210:253-260.
- 19) Mokdad AA, Murphy CC, Pruitt SL, et al. Effect of hospital safety net designation on treatment use and survival in hepatocellular carcinoma: HCC at Safety Net Hospitals. *Cancer* 2018;124:743-751.
- 20) Ladhani S, Ohri A, Wong RJ. Disparities in hepatocellular carcinoma surveillance: dissecting the roles of patient, provider, and health system factors. *J Clin Gastroenterol* 2020;54:218-226.
- 21) Harris PS, Hansen RM, Gray ME, et al. Hepatocellular carcinoma surveillance: an evidence-based approach. *World J Gastroenterol* 2019;25:1550-1559.
- 22) Wang S, Sun H, Xie Z, et al. Improved survival of patients with hepatocellular carcinoma and disparities by age, race, and socioeconomic status by decade, 1983-2012. *Oncotarget* 2016;7:59820-59833.
- 23) Farvardin S, Patel J, Khambaty M, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. *Hepatology* 2017;65:875-884.
- 24) Wang J, Ha J, Lopez A, et al. Medicaid and uninsured hepatocellular carcinoma patients have more advanced tumor stage and are less likely to receive treatment. *J Clin Gastroenterol* 2018;52:437-443.